

**U.S.S.N. 09/038,894
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PRELIMINARY AMENDMENT WITH RCE**

REMARKS

A check for the fee for a one month extension of time accompanies this response and for filing an RCE. Any fees that may be due in connection with filing this paper or with this application may be charged to Deposit Account No. 50-1213. If a Petition for extension of time is needed, this paper is to be considered such Petition.

Claims 10-18, 32-36, 38, 41 and 42 are presently pending in this application.

THE REJECTION OF CLAIMS 32-36, 38, 41, 42 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 32-36, 38, 41 and 42 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner alleges that the phrase "thereby preventing a disease" is allegedly not supported in the specification. The Examiner asserts that no data or other evidence can be found that such diseases would be prevented in animal models or other models and that, without such support, the claims are not enabled by the instant specification.

This rejection is respectfully traversed. As discussed below, the Examples demonstrate "prevention of a disease" by administration of cell activation lowering therapy.

The relevant law

In order to satisfy the enablement requirement of 35 U.S.C § 112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. Atlas Powder Co. v. E.I. DuPont de Nemours, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be

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satisfied by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything *within the scope* of a broad claim." In re Anderson, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of § 112, first paragraph "can be fulfilled by the use of illustrative examples or by broad terminology." In re Marzocchi et al., 469 USPQ 367 (CCPA 1971)(emphasis added).

Further, because "it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." In re Grimme, Keil and Schmitz, 124 USPQ 449, 502 (CCPA 1960). Thus, there is no doubt that a patentee's invention may be broader than the particular embodiment shown in the specification. A patentee not only is entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims that define the invention without a reference to specific instrumentalities. Smith v. Snow, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935).

Thus, there is no requirement for disclosure of every species within a genus. Applicant is entitled to claims are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed.

The inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require undue experimentation to make and use the claimed invention. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or

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guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

Analysis

As discussed below, applying the above factors to the instant claims demonstrates that it would not require undue experimentation to practice the claimed methods. It is respectfully submitted that in this instance in view of the scope of the claims and data and disclosure in the specification it would not require undue experimentation to practice the claimed methods. The application is directed to methods and compositions related to the finding that the activation status of neutrophils and other inflammatory cells is of central importance not only disease states, such as ischemia, infection, trauma, inflammatory diseases, but also in 'healthy' individuals. It is shown in the application that such cellular activation can be used as an indicator of therapeutic outcome and also as therapeutic target. Assays are performed on whole blood or leukocytes. The results of the assays can be used within a clinical framework to support therapeutic decisions, including but not limited to: further testing for infectious agents; anti-oxidant or anti-adhesion therapy; postponement and optimal re-scheduling of high- risk surgeries; classifying susceptibility to and progression rates of chronic disease such as diabetes, atherogenesis, and venous insufficiency; extreme interventions in trauma cases of particularly high risk; and activation-lowering therapies as yet to be developed.

Thus, the results of specific cell activation assays are used in guiding therapeutic decisions such as, but not limited to: further testing for infectious agents, anti-oxidant or anti-adhesion therapy, postponement and optimal re-scheduling of high- risk surgeries, classifying susceptibility to and progression

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rates of chronic disease such as diabetes, atherogenesis, and venous insufficiency; extreme interventions in trauma cases of particularly high risk and activation-lowering therapies.

Furthermore, methods of assessing treatment options and methods of treatment are also provided, and are claimed in the pending claims, in which cellular activation is measured, and, if elevated, activation lowering therapy is administered prior to undertaking any treatment for the particular disease or disorder. Activation lowering therapy methods include any method that lowers activation, including alterations in lifestyle, including stress management, exercise and diet, administration of drugs, such as heart medications, aspirin, administration of protease inhibitors, including Futhan (nafamostat mesilate, which is 6-amidino-2-naphthyl p-guanidinobenzoate dimethanesulfonate), as described herein.

Thus, in an individual exhibiting elevated levels of cell activation, the risk of a treatment can be reduced and treatment outcome can be improved for by treating the subject with agents that lower cell activation prior to or in conjunction with treating the actual disease. The observations and results presented in the application demonstrate that the risk of developing certain diseases and disorders, such as ischemic disorders, is reduced by treating the subject with agents that lower cell activation in advance of the disease or disorder.

Scope of the claims

Independent claim 32 is directed to a method of prophylaxis, diagnosis and treatment. The method requires the steps of assessing cell activation and, if elevated, administering activation lowering therapy, thereby preventing a disease or disorder or reducing the risk of a poor outcome of treatment of a disease or disorder. The specification provides that cell activation is pivotal in many chronic and acute diseases and conditions by initiating or contributing thereto (see, e.g., page 12, line 2 and page 42, lines 29-30) and **shows** that the

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level of cell activation is statistically correlated with the outcomes of treatment of disease states, such as, for example, cardiovascular diseases and disorders, inflammatory disease, shock, infection, trauma, autoimmune diseases, arthritis, diabetes and diabetic complications, stroke, ischemia, and Alzheimer's disease.

The specification also states that cell activation measurements can be used in guiding therapeutic decisions such as classifying susceptibility to and progression rates of chronic diseases such as diabetes, atherogenesis, and venous insufficiency (see, e.g., page 12, line 28 to page 13, line 2).

The specification further teaches that assessment of cell activation can be performed on healthy individuals that present no disease or disorder (see, e.g., page 12, line 6 and page 24, lines 22-30), and elevation thereof is predictive of the risk of development of disorders. Treatment of such individuals with cell activation lowering protocols lowers the risk of the developing such a disorder.

Since the specification teaches that cellular activation can play a causal role in many disease states and the scope of assessing cell activation includes its use in evaluating susceptibility to a disease or disorder in an otherwise healthy individual, the further step of administering activation lowering therapy in such embodiments is preventative.

The specification specifically teaches and demonstrates that cell activation lowering therapy, such as administration of protease inhibitors, such as futhan, can be administered for prophylactic purposes (see, e.g, page 42, line 31 to page 43, line 1). In all instances, the targeted underlying pathology is cell activation levels. If the levels of cellular activation are reduced, the risk of developing a disorder is reduced, or the risk of treatment of a particular condition is reduced and the outcome of such treatment is improved. The specification establishes that elevated levels of cell activation are associated with such treatment outcomes.

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Thus, the scope of enablement provided by the disclosure of the specification is commensurate with the scope of protection sought in the claims. As provided below, the teachings of the specification enable one skilled in the art to make and use the entire scope of the claimed methods without undue experimentation.

The quantity of experimentation necessary

To practice the method as claimed one of skill in the art only has to test for the level of cell activation and administer cell activation lowering therapy if it is elevated. Such measurements are performed prior to any further therapy or as a prophylactic.

The specification provides procedures assaying cell activation levels and methods for lowering cell activation levels. For example, at page 12, the specification teaches cell activation can be "assessed [by] superoxide production, such as as defined by the nitroblue tetrazolium test and lucigenin-enhanced chemiluminescence, and/or actin polymerization, such as defined by the pseudopod formation test." Starting at page 26, the specification describes a variety of exemplary cell activation assessment assays:

The tests, discussed and exemplified below in more detail below and include tests that assess indicators of activation, such as changes in shape and free radical production. For example cell morphological changes may be quantified with direct microscopic examination, with or without fluorescent staining of F-Actin filaments present in pseudopods, or with fluorescence activated cell sorting techniques. Superoxide anion production can be detected and quantified using chemiluminescence generating reagents, such as luminol, isoluminal and lucigenin, that quantitatively react therewith. Free radicals can be assessed by NBT (nitroblue tetrazolium). Adhesion can be assessed by various immunassays that detect surface adhesion molecules, such as CD11, CD18 and L-selectin and others. Other indicators of activation include expression of certain factors, such as interleukin and TNF- α , which can be measured by known immunoassays.

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Activation can also be assessed by sampling plasma and determining whether it activates cells, such as endothelial cell cultures. Plasma can be tested for clastogenic activity by standard methods. Although there is a high correlation between the different cell activation assay measures, it is likely that there will be different combinations of indicators which are most informative in any situation. For example, plasma activator levels might be high but circulating activated neutrophil counts low due to sequestration of the activated cells in the microcirculation. Also, genetic, age, and environmental differences between patients will complicate the interpretation of the assays. Clinical tests are in preparation to relate statistically cell activation measures to disease outcomes, to find the formulas which are invariant to patient differences, and to establish the best predictive procedures and activation lowering therapies in different situations. The measurement of cell activation and circulating plasma factors also serves as an effective tool to evaluate the effectiveness of new interventions prior to execution of full-scale clinical trials. Drug candidates thereby may be rejected, or patient populations enriched for more favorable response to the candidate drug.

Detailed cell activation protocols are described in Section E (page 35 *et seq.* of the specification.

Rates of free radical production in whole blood can be measured using phenol red (Pick *et al.* (1980) J. Immunol. Methods 38:161-170) or other dye forming reagents (U.S. Patent No. 5,518,891). Intracellular radical production may be measured with nitroblue tetrazolium (NBT) reduction or chemiluminescence (Cheung *et al.* (1984) Aust. J. Expt. Biol. Med. Sci. 62:403) assays. Radical production in whole blood or plasma may be measured electrochemically, and mRNA expression of specific genes can be quantitated, for example, using Northern blots or DNA microarrays.

Expression of adhesion molecules such as CD11b, CD18, and of L-Selectin can be quantitated via flow cytometry, while cytokines and chemokines, such as interleukins and TNF- α can be quantitated with immunoassays.

Cell morphological changes may be quantified with direct microscopic examination, with or without fluorescent staining of F-Actin filaments present in pseudopods, or with fluorescence activated cell sorting techniques.

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Blood plasma is known to carry cell activation factors in response to specific events. Plasma from I/R episodes including MI (Chang *et al.* (1992) *Biorheology* 29:549-561) and hemorrhagic shock (Elgebaly *et al.* (1992) *J. of Thoracic and Cardiovascular Surgery* 103(5):952-959; Paterson *et al.* (1993) *Am. Vasc. Surg.* 7(1):68-75; Barroso-Aranda *et al.* (1995) *J. Cardio Pharmacology* 25(Suppl 2):S23-S29) activates neutrophils, as does plasma from smokers' blood (Pitzer *et al.* (1996) *Biorheology* 33(1):45-58). Patient blood samples can be applied to standard donor cells and the response of the donor cells used as a measure of the potency of the circulating activating factors in the patient blood.

The specification provides working examples (see, *e.g.*, EXAMPLES 1, 2 and 6), including description of the an electrode method for measuring hydrogen peroxide, which is correlated with cell activation levels.

The specification also describes an array of cell activation lowering protocols (see, *e.g.*, page 13), such as stress management, exercise and diet, administration of drugs, such as heart medications, aspirin, administration of protease inhibitors, including Futhan (nafamostat mesilate, which is 6-amidino-2-naphthyl p-guanidinobenzoate dimethanesulfonate).

The Examples demonstrates in an animal model that lowering of cell activation can prevent a disease or improve the outcome. For instance, Example 8 (page 136 to 144) provides models of disease states and detailed experiments for assessing the ability of cell activation lowering therapy to prevent a disease. The assays and treatment protocols employed in Example 8 as well as numerous other cell activation assays, drug screening assays and treatment protocols are discussed in detail in the specification (see, *e.g.*, pages 35, 36, and 37-47, Example 6, and Example 3, particularly 3.1d and 3.2). Given the detailed procedures provided throughout the specification, including the the Examples, minimal experimentation is needed to practice the method.

Teachings of the Specification

As discussed above, the instant specification provides ample direction and guidance to one skilled in the art as to how to use the method of the instant claimed methods. As described above, the specification teaches methods for measuring cell activation and methods for lowering the levels of cell activation, thereby teaching all elements of the methods as claimed.

Furthermore, the specification exemplifies various applications in which assessment of cell activation can be used and in which cell activation lowering therapy can be administered as well as the types of diseases and disorders that can be prevented or for which the risk of treatment outcome can be reduced. As shown in Figure 2 and described on page 24 of the specification, activation levels can be measured in a seemingly healthy patient:

If low, then no treatment or changes in lifestyle are recommended. If the levels are elevated (above the 50th percentile, more likely above the 20th percentile, or one standard deviation above the mean or more), then tests to determine the presence of subclinical infection or other cell activating condition are performed. If those tests are negative, then lifestyle and diet should be examined, and if, necessary, modified. If diet is good, and lifestyle is generally good and stress-free, then activating lowering therapy can be instituted.

As described in the specification, this diagnostic measure permits early intervention. Administering activation lowering therapy to healthy individuals identified as having elevated levels of activated cells with no other indications of a disease or disorder is a preventative measure. As indicated in the specification, inappropriate or chronic presence of increased cell activation can initiate disease states. In addition, as presented below, the specification provides detailed experiments including specific experiments with animal models.

Presence of working examples

The specification provides a substantial amount of guidance and includes a number working examples with *in vitro* and *in vivo* data demonstrating the effectiveness of cell activation lowering agents. The specification also provides assays for identifying effective cell activation lowering agent, particularly protease inhibitors.

As shown in the application the level of cell activation, particularly neutrophil activation, is an indicator of therapeutic outcome and also serves as therapeutic target. The specification provides *in vitro* and *in vivo* data demonstrating that the level of cellular activation plays a critical role in the outcome of various disease states and that treatment with cell activation lowering agents can improve treatment outcomes of disorders, and also prevent the disorders. The specification also shows that cellular activation is an effective therapeutic target and demonstrates that certain cell activation lowering therapy, including protease inhibitors can lower cell activation.

The specification shows (see, *e.g.*, Example 7) that the neutrophils are implicated in the pathogenesis of a number of disease processes acute and chronic and their inappropriate upregulation (cell activation) is a predisposing risk factor for disease in otherwise healthy individuals.

As shown in the specification, plasma taken from animals and clinically after ischemic events display the ability to activate naive neutrophils, indicating that a circulating humoral factor is in part responsible for the upregulation of neutrophils and inflammation seen after these events. The presence of such an activator in rat shock plasma, is identified in the application and shown to be produced endogenously by the pancreas, which, alone of all organs studied, possesses an inherent ability to activate neutrophils *in vitro*. Further studies characterize properties of this factor *in vitro* and *in vivo*, and many of the physiological properties of the pancreatic neutrophil activator(s) have been determined.

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The specification (see Examples) also shows that a pancreatic homogenate is a potent cell activator and that activation is inhibited by addition of protease inhibitors. The homogenate is shown to serve as a screening tool for identifying agents that inhibit cell activation, including proteases (see, *e.g.*, pages 29-33). As shown in the application, when incubated with homogenates of other organs, the pancreatic homogenate supernatant, and also trypsin and chymotrypsin, cause cell-activating factors to be released from these other homogenates. Serine protease inhibitors and others that were tested inhibit production of the cell activating factors in *in vitro* experiments and reduce systemic responses *in vivo*. Other experiments showed that other tissues could be made excitatory towards neutrophils by the addition of limited concentrations of pancreatic homogenate or serine proteases.

Protease inhibitors are shown in the application to mitigate neutrophil activation *in vitro* and *in vivo* in animals. Mortality in animals subjected to either SAO shock or injected with pancreatic homogenate was reduced or prevented by pre-treatment with a protease inhibitors (see discussion of Example 8 below). A number of protease inhibitors were studied for their ability to inhibit pancreatic homogenate-induced neutrophil activation and shown to be active. As shown in Example 7 in the specification, administration of protease inhibitors as assessed by neutrophil pseudopod formation by rat pancreatic homogenate, resulted in a decrease in neutrophil activation that varied depending on protease inhibitor used.

As a control set of experiments, sub-activating concentrations of pancreatic homogenate were added to other organ homogenates liver, spleen, intestine, and heart that had previously shown little neutrophil activating ability. Surprisingly, incubation of these tissues with low concentrations of pancreatic homogenate resulted in their ability to strongly activate neutrophils. Further experiments demonstrated that this ability to activate neutrophils by previously inert organ homogenates could be duplicated by the addition of the pancreatic

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proteases chymotrypsin or trypsin. Neither chymotrypsin nor trypsin intrinsically activate neutrophils *in vitro*, and heart, liver, spleen, and intestine homogenates have been shown to be non-stimulatory toward neutrophils. The addition of the proteases, however, resulted in the ability of these tissues to activate neutrophils *in vitro*. Hence, protease inhibitors should prevent this effect.

To relate the *in vitro* results obtained with pancreatic homogenate on neutrophil activation and its inhibition by proteases to the *in vivo* state, the SAO shock experiments were repeated using Futhan pretreatment in animal models. After optimal concentration and infusion parameters were determined, 60 minutes pretreatment of Futhan was found to mitigate the decrease in mean arterial pressure (MAP) seen after reperfusion (unclamping) in SAO shock. Mortality was reduced acutely and plasma levels of peroxide production were significantly lower than in saline-treated control rats. The mechanism of protection by Futhan appears to be due to a number of factors, including reducing neutrophil activation *in vivo*, stabilization of pancreatic lysosomal and acinar membranes, and an overall increase in the protective circulating anti-protease screen.

Injection of filtered pancreatic homogenate into animals closely simulated the MAP of the reperfusion phase in SAO shock, and resulted in increased circulating peroxide production as well immediate death, as seen in SAO shock. Pretreatment of healthy animals with Futhan before initiating the shock protocol increased MAP in response to pancreatic homogenate injection and abolished the mortality seen in untreated animals, demonstrating that protease inhibitor treatment can prevent and/or reduce the risk of developing shock. Injection of the low-molecular weight component of pancreatic homogenate also resulted in a sharp decrease in MAP. Blood pressure in these animals however, recovered after an approximately 10 minute hypotensive period and animals **did not go**

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into shock at the concentrations given (a maximum of 30% of the low-molecular weight component of one pancreas/animal).

The Examiner alleges that the specification provides no data or other evidence to support prevention of a disease or disorder in animal models or other models. The Examiner insists that without such support, the claims are not enabled by the instant specification.

Contrary to the Examiner's assertion, Example 8 of the specification (pages 136-145) as described in detail above provides support with animal models. This Example provides results of detailed experiments employing Splanchnic Arterial Occlusion (SAO) shock models (effected either by arterial clamping or by bolus injection of pancreatic homogenate). In these experiments, animals pretreated with a serine protease such as Futhan were compared with saline-pretreated control animals. The results show that performance of SAO shock protocols on saline-pretreated control animals resulted in uniform hypotension (shock) and death. In animals pretreated with serine protease, shock and mortality was prevented. Only a transient decrease in blood pressure or at most a brief hypotension was reported (see, e.g., page 32, lines 15-16; page 137, line 25 to page 138, line 2; and page 144, line 20)). Thus, Example 8 provides detailed SAO shock models and ample evidence to support the prevention of disease by administration of activation lowering therapy as required by the claims.

Level of skill

The level of skill in this art is recognized to be high (see, e.g., Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986)). The numerous articles and patents made of record in this application address a highly skilled audience and further evidence the high level of skill in this art.

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Knowledge of those of skill in the art

At the time of the effective filing date of this application and before, the skilled artisan knew that cells in microcirculation can be encountered in a relatively quiescent state and in various stages of activation. It was also known that cell activation is a normal physiological response that is essential for survival from infection and is brought about by certain cellular activating factors. It was also known that inappropriate activation is implicated in the pathology of many disease processes. In particular, there was evidence that cardiovascular complications, such as myocardial infarction, venous ulceration and ischaemia/reperfusion injury may be associated with an activation of cells in circulation such as neutrophils and other inflammatory cells. Further, there was a large body of literature, incorporated in the instant specification by reference (see, e.g., pages 5-10), that was directed to the identification of factors responsible for cellular activation. Hence, the skilled artisan, in light of the teachings of the instant application, had an entire body of knowledge from which to draw and apply it as claimed in the instant application.

Furthermore, as discussed above, there were numerous assay available and known to those of skill in the art for assess cell activation (not for the instantly claimed purposes, but nevertheless applicable to the instantly claimed methods) Others of the assays provided in the application were well known, although not necessarily for disclosed purpose of assessing cellular activation. For instance, phenol red assays (Pick et al. (1980) J. Immunol. Methods 38:161-170), nitroblue tetrazolium and chemiluminescence assays (Cheung et al. (1984) Aust. J. Expt. Biol. Med. Sci. 62:403) were known to those of skill in the art at the time the application was filed.

Predictability

The instant application teaches that the measurement of cell activation is a diagnostic and prognostic indicator, and that the level of cell activation is a therapeutic target for improving treatment outcomes and preventing or reducing

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risk. Once one of skill in the art is taught this connection, the claimed methods can be practiced and their result is predictable, since the instant application associates disparate observations.

As discussed above, the involvement of processes of cell activation in a wide array of diseases was known, assays that can be used to measure cell activation were known, and protocols for reducing cell activation (or for other purposes) were known. The instant application teaches that reduction of cell activation in healthy or ill or injured subjects can improve treatments and reduce risk. The instant application and methods explain why, when two patients with comparable illnesses or injuries and treatments can have such different outcomes.

Conclusion

Therefore, in light of the scope of the claims, which are tailored to the scope of the disclosure, the extensive description in the application, the *in vitro* and *in vivo* data provided in the specification and the high level of skill of those in this art, it would not require undue experimentation to practice the methods as claimed.

Applying the above factors to the instant application demonstrates that the specification enables those skilled in the art to make and use the claimed subject matter without undue experimentation. As explained above, the amount of direction and guidance in the specification is extensive. Applicant has provided animal models that demonstrate a prophylactic effect of cell activation lowering therapy, detailed protocols for administration of activation lowering therapy, and numerous assays for assessing cell activation. Furthermore, the quantity of experimentation necessary is minimal because the relative skill of those in the art is high and the predictability of the art is well known. Therefore, the specification enables those of skill in the art to make and use the claimed subject without undue experimentation.

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THE REJECTION OF CLAIMS 10-18, 32-36, 38, 41 and 42 UNDER 35 U.S.C. §103

Claims 10-18, 32-36, 38, 41 and 42 are rejected under 35 U.S.C. 103 as being unpatentable over Okada *et al.* ((1991) *Journal of International Medical Research* 19:234-236) (Okada 1), Okada *et al.* ((1991) *Journal of International Medical Research* 19:348-350) (Okada 2), Yanamoto *et al.* or Yonekura *et al.* in view of Gibboni *et al.*, Babcock *et al.*, and Brunck *et al.* because applicant is allegedly claiming a method of treating or preventing disorders using a protease inhibitor, and Okada 1, Okada 2, Yanamoto, and Yonekura allegedly teach administering futhan, to a patient. Gibboni and Pick are each alleged to teach that assays using phenol red are well known to be used for the measurement of hydrogen peroxide produced by cells in culture and, thus, the measurement of free radical production. Gibboni also is alleged to teach that such assays are useful for patients to check their cholesterol or glucose levels. Babcock is alleged to teach that traumas can be treated by administering compounds that scavenge free radicals. Brunck is alleged to teach that trauma, such as pancreatitis, is known to be treated by futhan.

In the instant Office Action, the Examiner contends that the arguments set forth in the Amendment filed October 28, 2002 in response to the Office Action dated July 26, 2002 were not persuasive because they attacked the references individually rather than as a combination. The Examiner provides no rebuttal to the specific arguments and asserts that the reasons for the rejection were presented in the previous Action. Without providing any support from the cited references, the Examiner concludes that it is clear from the record that a patient that was going to be treated for a disease would (1) have normal levels checked including, for example, blood pressure and glucose levels to rule out certain other problems; and (2) having checked glucose levels, the Examiner alleges that one would have also checked free radical production.

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The Examiner relies on the reasons for rejection presented in the Action dated July 26, 2002 as outlined below. Again without any particular references to the cited art, the reasons are as follows:

The Examiner states that since such patients would normally check their glucose levels, they would be motivated to treat their glucose overproduction if the levels were too high. Similarly, the Examiner reasons that someone who had a trauma would want to know before that condition was treated (if it needed to be treated) by futhan whether or not free radical production had occurred. The Examiner is of the opinion that it would have been within the purview of the skilled artisan to administer the phenol red assay first to detect the free radical production and, if elevated, the measurement would indicate that treatment for the trauma would need to be performed. Such treatment would be the administration of futhan.

In addition, again without citing any art, the Examiner reasons that, if someone has a trauma, such as pancreatitis, which is known to be treated by administering futhan, it would have been well within the purview of the "skilled artisan" to treat a trauma with futhan and to assess the treatment to see if it was necessary by using the phenol red assay since it is well known that phenol red assays are used to detect free radical production and that traumas are treated by compounds such as futhan and further that traumas are treated by compounds that scavenge free radicals.

The Examiner further reasons that since traumas are treated with futhan and traumas produce free radicals, it would have been obvious to use a compound like futhan after the detection of elevated free radical production by phenol red assay, to treat the patient in an effort to reduce the free radical production.

This rejection is respectfully traversed.

As discussed below, the claimed methods include the steps of assessing cell activation to determine whether it is elevated and if it is elevated

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administering cell activation lowering therapy. The cell activation therapy, such as futhan, is not administered to as treatment for any particular disease.

The Office Action has failed to set forth a case of *prima facie* obviousness

Relevant law

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (*ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577, 221 U.S.P.Q. 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. *Ex parte Gerlach*, 212 U.S.P.Q. 471 (Bd. App. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art" (*In re Keller*, 642 F.2d 413, 425, 208 U.S.P.Q. 871, 881 (CCPA 1981)), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (*ACS Hosp. Systems, Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 U.S.P.Q. 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 U.S.P.Q. 303, 312-13 (Fed. Cir. 1983). Importantly, **all claim limitations** must be taught or suggested by the prior art to establish that claims are *prima facie* obvious. See, e.g., MPEP 2143.03 and *In re Lowry*, 32 F.3d 1579, 32 U.S.P.Q.2d 1031 (Fed. Cir. 1994), citing *In re Gulack*, 703 F.2d 1381, 217 U.S.P.Q. 401 (Fed. Cir. 1983), citing *In re Royka*, 490 F.2d 981, 180 U.S.P.Q.2d 580 (CCPA 1974).

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Analysis

The Claims

Claim 10 is directed to a method of improving treatment outcome or reducing risk of treatment by assessing treatment options by:

- 1) measuring cell activation levels in a subject;
- 2) if cell activation levels are elevated, administering activation lowering therapy **prior** to commencing any treatment for the disease or condition. The cell activation therapy, such as administration of futhan, is **not** the treatment for a disease or condition, but refers to testing and therapy to be administered **before treating a disease or condition.**

Claim 32 is directed to a method of prophylaxis, diagnosis and treatment, including the steps of assessing cell activation; and, if elevated, administering activation lowering therapy, thereby preventing a disease or disorder or reducing the risk of a poor outcome of treatment of a disease or disorder.

It is respectfully submitted that the rejection appears to be based on a misunderstanding of the elements of the claimed methods. As described in the application on page 16, lines 19-25, cell activation refers to changes in and interactions among circulating white blood cells, including leukocytes, cells lining blood vessels, including endothelial cells, and platelets. These changes are evidenced by increased "stickiness" of cells, changes in shapes of cells, free radical production, release of inflammatory mediators and enzymes, pseudopod formation, and expression of adhesion molecules.

As shown and described in the application, increased levels of cell activation can adversely impact treatments of diseases, and for example, explain why one patient suffering from a disease or injury survives surgery, whereas another with the same disease or injury does not. The application shows that high levels of cell activation influence disease treatment outcomes, and hence, should be used in assessing treatment options, and also, where possible, should

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be reduced prior to treatment or simultaneously with treatment for a particular disorder.

The methods of the claims assess the level of cell activation by measuring indicators thereof. If the levels are elevated, then treatment to lower cell activation (administration of activation lowering therapy) is initiated. The activation lowering therapy is not treatment for a particular disease. The step of administering activation lowering therapy is either prior to (or simultaneous with) treatment for a particular disease or disorder. Such treatment as shown in the application can improve treatment outcome or reduce risk of treatment (claim 10), or can be prophylactic where there is no evidence of disease or can improve the risks of treatment (claim 32).

Differences Between the Claims and the Combination of Teachings of the Cited References

Okada 1 and 2

The Okada references teach that complement activation is involved in insulin-dependent diabetes mellitus and that futhan is an inhibitor of complement activation. Okada 1 teaches that futhan lowers cytotoxicity activity of sera as measured by chromium release assay. Okada 1 does not teach assessment of cell activation nor administration of futhan to lower cell activation, nor does Okada 1 teach or suggest a method in which cell activation is assessed and, if elevated treated, as way of preventing disease, improving treatment outcome, or reducing the risk of treatment. None of the remaining references cure these deficiencies.

Okada 2 presents a study of the effect of futhan on complement activation in an adult male with insulin-dependent diabetes mellitus and provides evidence of complement activation in insulin-dependent diabetes mellitus. Okada 2 does not teach assessment of cell activation. Further, Okada 2 does not teach or suggest administration of futhan to lower cell activation, or a method in which cell activation is assessed and, if elevated, treated as a way of

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preventing disease, improving treatment outcome, or reducing the risk of treatment. Thus Okada 2 does not cure any deficiencies of Okada 1.

Yanamoto *et al.*

Yanamoto *et al.* reports the therapeutic effect of futhan for treating cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Yanamoto *et al.* does not teach or suggest assessment of cell activation nor the administration of cell activation lowering therapy. The administration of Futhan in Yanamoto *et al.* is for the treatment of a particular disease, not to lower cell activation. Yanamoto *et al.* does not teach a method in which cell activation levels are assessed, and, if elevated, treated as a way of preventing disease, improving treatment outcome, or reducing the risk of treatment. The reference only teaches that futhan can be used to treat cerebral vasospasm, thus, Yanamoto *et al.* does not cure any of the deficiencies of Okada 1 and 2.

Yonekura *et al.*

Yonekura *et al.* teaches the effects of treatment of disseminated intravascular coagulation (DIC) with futhan. Yonekura *et al.* teaches that futhan inhibits proteinases of the coagulation, fibrinolysis, Kallkrein kinin and complement systems. Yonekura *et al.* does not teach or suggest assessment of cell activation nor the administration of cell activation lowering therapy if cell activation is elevated. The administration of Futhan in Yonekura *et al.* is for the treatment of a particular disease, not to lower cell activation. Yonekura *et al.* does not teach a method in which cell activation levels are assessed, and, if elevated, treated as a way of preventing disease, improving treatment outcome, or reducing the risk of treatment. The reference only teaches that futhan can be used to treat disseminated intravascular coagulation, thus, Yonekura *et al.* does not cure any of the deficiencies of Okada 1, Okada 2, and Yanamoto *et al.*

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Gibboni *et al.* and Pick *et al.*

Each of Gibboni *et al.* and Pick *et al.* teaches the use of phenol red assays for the measurement of hydrogen peroxide. Pick *et al.* teaches a method for assessment of hydrogen peroxide produced by cells in culture. Pick *et al.* does not mention cell activation whatsoever, nor use of the phenol red assay to measure cell activation.

Gibboni *et al.* teaches dyes for use in detecting hydrogen peroxide in a sample. As with Pick *et al.*, Gibboni *et al.* does not mention cell activation whatsoever and, thus, does not teach or suggest the use of its dyes to measure cell activation.

Neither Gibboni *et al.* nor Pick *et al.* teaches or suggest that measurement of hydrogen peroxide can be used as a measure of cell activation. The references do not discuss treatment of any kind and, thus, do not teach or suggest administration of any treatment as a means of preventing disease, improving treatment outcome, or reducing the risk of treatment, nor do that teach or suggest a methods in which levels of cell activation are assessed, and if elevated, treatment for reduction thereof is administered. Thus, Gibboni *et al.* and Pick *et al.* do not cure any of the deficiencies of Okada 1, Okada 2, Yanamoto *et al.*, and Yonekura *et al.*

Babcock *et al.*

Babcock *et al.* teaches the use of aminosteroids for prophylaxis and treatment of ophthalmic diseases or disorders. The compounds are used to treat oxidative intraocular damage by arresting oxidative processes that cause damage to the eye.

Babcock *et al.* does not mention cell activation whatsoever, nor a method in which cell activation is assessed, and if elevated, treated by administering cell activation lowering therapy to prevent disease, improve treatment outcome, or reduce the risk of treatment. The methods and compositions provided by Babcock *et al.* can be used to prevent diseases and

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disorders but not by lowering cell activation. It is stated that the compounds of Babcock *et al.* arrest oxidation processes. Babcock *et al.* does not teach or suggestion that these oxidative process are, in any way, related to cell activation. Thus, Babcock *et al.* does not cure any of the deficiencies of Okada 1, Okada 2, Yanamoto *et al.*, Yonekura *et al.*, Gibboni *et al.* or Pick *et al.* and is of very little relevance to the claimed subject matter.

Brunck *et al.*

Brunck *et al.* teaches compounds, such as futhan, that have activity as inhibitors of pancreatic trypsin, and their use in the prevention and treatment of the tissue damage or destruction associated with pancreatitis resulting from digestive enzymes activated by trypsin. Brunck *et al.* teaches that digestive enzymes activated by trypsin are elevated in pancreatitis.

Brunck *et al.* does not mention cell activation. Brunck *et al.* does not teach or suggest a method in which cell activation levels are assessed, and if elevated, therapy to lower the levels is administered before administering treatment for a disease or disorder improve treatment outcome, or reduce the risk of treatment or as a prophylactic measure. As with all of the cited references the steps of assessing cell activation and administering cell activation lowering therapy (as a treatment to reduce cell activation) prior to treatment for a disease or for prophylactic purposes is not taught or suggested.

Thus, as described in more detail below, the combination of teachings of the cited does not result in the instantly claimed methods. None of the references, singly or in any combination thereof, teaches or suggests a method in whcih cell activation levels are assessed, and if elevated, therapy to lower the levels is administered.

As addressed below, there is no motivation to combine Okada 1, Okada 2, Yanamoto or Yonekura with Gibboni or Pick, and Babcock, and Brunck. Notwithstanding this failure, even if there had been motivation to combine Okada 1, Okada 2, Yanamoto or Yonekura with Gibboni or Pick, and Babcock,

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and Brunck, the combination fails to teach to suggest all of the elements of the claimed methods.

The Combination of Teachings of Okada 1, Okada 2, Yanamoto or Yonekura with Gibboni or Pick, Babcock, and Brunck Fails to Result in the Claimed Methods

None of the references teaches or suggests a method that includes the steps of assessing cell activation levels, and, if elevated administering cell activation lowering therapy prior to (or with) administering treatment for a disease or disorder or prophylactically.

(D)

Yanamoto teaches treatment of cerebral vasospasm after aneurysmal subarachnoid hemorrhage with futhan; Yonekura *et al.* teaches the effects of treatment of disseminated intravascular coagulation (DIC) with futhan; Babcock *et al.* teaches the use of aminosteroids for arresting oxidation processes and prophylaxis and treatment of ophthalmic diseases or disorders; Brunck *et al.* teaches compounds that have activity against trypsin, such as futhan, for the treatment of the tissue damage or destruction associated with pancreatitis.

These references fail to teach or suggest a method of improving treatment outcome or reducing risk of treatment, by assessing treatment options for a disease or condition by measuring cell activation levels in a subject; and, if elevated, administering activation lowering therapy prior to commencing further treatment for the disease or condition, thereby improving treatment outcome or reducing risk of treatment; nor a method of prophylaxis, diagnosis and treatment by assessing cell activation; and, if elevated, administering activation lowering therapy, thereby preventing a disease or disorder or reducing the risk of a poor outcome of treatment of a disease or disorder.

None of these references, singly or in any combination, teaches a step of measuring cell activation levels to assess whether they are elevated, nor a method in which if cell activation levels are elevated, initiating cell activation lower therapy. In all references in which futhan is administered, it is

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administered as the treatment for a disease, not for cell activation lowering therapy, and certainly not following assessment of cell activation to determine if the level is elevated.

Neither Gibboni *et al.* nor Pick *et al.* cure these deficiencies. Each of Gibboni *et al.* and Pick *et al.* teaches an assay for measuring hydrogen peroxide. Neither reference teaches or suggests assessing the levels of cell activation to determine if they are elevated nor administering cell activation lowering therapy if the levels are elevated. Neither reference, singly or in combination, teaches or suggests administering treatment to lower cell activation, if cell activation levels are high. The steps of the claimed methods are either prior to treatment for a particular disease (claim 10), or are prophylactic (claim 32) where there is no evidence of disease or as way to improve the risks of poor outcome of treatment (claim 32).

Therefore, the combination of teachings of the references does not result in the instantly claimed methods. No combination of teachings of any or all of the cited references teaches or suggests a method (claim 10) of improving treatment outcome or reducing risk of treatment by assessing treatment options by:

- 1) measuring cell activation levels in a subject; and
- 2) if cell activation levels are elevated, administering activation lowering therapy **prior** to commencing any treatment for the disease or condition. The cell activation therapy, such as administration of futhan, is **not** the treatment for a disease or condition, but refers to therapy to be administered **that is distinct from the treatment of a disease or condition.**

No combination of teachings of any or all of the cited references teaches or suggests a method a method of prophylaxis, diagnosis and treatment (claim 32), by assessing cell activation; and, if elevated, administering activation lowering therapy, thereby preventing a disease or disorder or reducing the risk of a poor outcome of treatment of a disease or disorder.

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Thus, the combination of teachings of the cite reference does not result in the instantly claimed methods. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

There was no Motivation to Have Combined the Teachings of Okada 1, Okada 2, Yanamoto or Yonekura with Gibboni or Pick, Babcock, and Brunck

Notwithstanding the above, not only does the combination of teachings of the references not result in the claimed methods, there was no motivation or suggestion from the references that would have lead to any combination of the references absent the teachings of the instant application. Each of the references teaches a unique method, separate and complete in itself; there is no teaching in the references related to futhan therapy that links them to the references that teach methods of measuring free radical production.

The Okada references illustrate a method of treating insulin-dependent diabetes mellitus by administering futhan. Yanamoto *et al.* reports the therapeutic effect of futhan for treating cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Yonekura *et al.* teaches the effects of treatment of disseminated intravascular coagulation (DIC) with futhan. There is no motivation to combine any of these methods of using futhan with the methods of Gibboni *et al.*, Pick *et al.*, Babcock *et al.* and/or Brunck *et al.*. Each of Gibboni *et al.* and Pick *et al.* teaches a method for measuring hydrogen peroxide. There is no motivation or suggestion from the references to measure free radical production prior to delivering futhan. The Okada references, Yanamoto *et al.* and Yonekura *et al.* teach treatments that happen to result in cell activation lowering, but they do not teach that this is the effect of futhan or any other therapy; rather futhan is administered to treat a particular disorder. None teach or suggest measurement of cell activation levels, and none teach or suggests lowering cell activation if cell activation levels are elevated.

Brunck *et al.* teaches that futhan inhibits trypsin and, thus, futhan can be administered to treat pancreatitis caused by trypsin damage. As with Okada

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(1), Okada (2), Yanamoto *et al.* and Yonekura *et al.*, there is no suggestion that futhan lowers cell activation. Further, Brunck does not teach or suggest the measurement of cell activation levels prior to administering futhan. Nor does Brunck teach or suggest the administration of futhan prior to administering treatment for a disease to improve treatment outcome, or reduce the risk of treatment. There is also no suggestion of a method of prophylaxis.

Babcock *et al.* teaches a method of treating a particular disease, not a precursor (high levels of cell activation) to a disease. Babcock teaches the use of aminosteroids for arresting oxidation processes in the eye for preventing or treating ophthalmic diseases or disorders, but does not suggest methods in which cell activation levels are measured prior, and if elevated, cell activation lowering therapy is administered prior to commencing therapy for a disease. Babcock *et al.* states that its methods and compositions may be used to prevent diseases and disorders but not by lowering cell activation. It is stated that the compounds of Babcock *et al.* arrest oxidation processes. Babcock *et al.* does not teach or suggestion that these oxidative process are, in any way, related to cell activation. Further, Babcock *et al.* does not teach or suggest a method of improving treatment outcome or reducing risk of treatment, by first measuring cell activation levels, and, if they are elevated administering cell activation lowering therapy. Babcock *et al.*, as the Okada references Yanamoto *et al.*, Yonekura *et al.*, and Brunck *et al.*, is directed to methods of treating particular diseases. None of the references teaches or suggests methods of treating cell activation as a precursor to treatment for disease or as a prophylactic measure.

Gibboni *et al.* and Pick *et al.* do not teach or suggest the measurement of cell activation as part of a therapeutic protocol, and none suggest such combination. Gibboni *et al.* and Pick *et al.* are each directed to particular assays to measure hydrogen peroxide.

Thus, there is no motivation from the teachings of the references to have combined the teachings of Okada (1), Okada (2), Yanamoto *et al.* Yonekura *et*

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al. and/or Brunck *et al.* with those of Gibboni *et al.* and/or Pick *et al.* These references do not teach that futhan can be used to lower cell activation. More importantly, as already addressed above, even if there was motivation to combine the cited references, the combination of references does not result in the claimed methods.

The Combination of References is based on Hindsight

"To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 U.S.P.Q. 303, 312-13 (Fed. Cir. 1983).

The teachings of the combination of references do not result in the instantly claimed methods. For the combination of teachings to result in the methods as claimed, requires use of the teachings of the application at issue. To produce the claimed methods, requires picking and choosing portions of methods taught in the cited references, combining them as claimed in the application and adding teachings of the instant application. The claimed methods are not prima facie obvious because the combination of teachings of the references does not result in the instantly claimed methods.

For example, it is inappropriate for the Examiner to pick the part of the method of Gibboni and Pick that relies on the measurement of hydrogen peroxide and conclude that because methods of measuring hydrogen peroxide are known, that it is obvious to use them to assess whether cell activation levels are elevated. None of the references provides motivation to modify such an assays to assess whether cell activation levels are elevated. The Examiner has, therefore, relied on what is taught by the instant application.

Furthermore, it is inappropriate for the Examiner to pick the part of the method of Babcock that relies on treating ophthalmic diseases with compounds

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that scavenge free radicals and the portion of Brunck that relies on treating pancreatitis with futhan to arrive at the conclusion that, "since traumas are treated with futhan and traumas produce free radicals, it would have been obvious to use a compound like futhan after the detection of elevated free radical production, to treat that patient with futhan in an effort to reduce the free radical production." None of the references teaches detecting elevated free radical production as a means to assess cell activation, and then, if elevated, administering treatment to reduce cell activation. Therefore, the Examiner has improperly relied on hindsight in setting forth the rejection, has failed to recognize the actual elements of the claimed methods, and has failed to set forth a *prima facie* case of obviousness.

REBUTTAL TO SPECIFIC ARGUMENTS FROM ACTION DATED JANUARY 27, 2003 SET FORTH BY THE EXAMINER IN RESPONSE TO APPLICANT'S TRAVERSAL IN THE AMENDMENT FILED OCTOBER 28, 2002

1) The Examiner alleges that in the Amendment and Response filed October 28, 2002, Applicant attacked the cited references individually, and that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references.

It is respectfully submitted that the response did not address the cited references individually in rebuttal of the rejection set forth under 35 U.S.C. § 103(a). Rather, the response systematically (i) distinguished the teachings of each of the cited references from the instantly claimed subject matter; and (ii) showed that the deficiencies of each of the cited references against the claimed subject matter was not cured by any of the other cited references. The references were then combined and the response demonstrated that combination of teachings of the references does not teach or suggest the claimed subject matter.

The Examiner is referred to page 6 of the Amendment and Response filed October 28, 2002, in which the section entitled:

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"Differences between the claims and the teachings of the cited references"

discusses how the combination of the cited references does not result in the claimed subject matter because, among other reasons of record in the aforementioned Amendment, all the cited references lack a teaching or suggestion of the instantly claimed elements of assessing cell activation and administering cell activation lowering therapy (as a treatment to reduce cell activation not a treatment for an underlying disease) prior to treatment for a disease or for prophylactic purposes. Thus, the cited references, singly or in any combination thereof, fail to teach or suggest all elements of the claims.

The Examiner is further referred to page 10 of the Amendment and Response filed October 28, 2002, in which the section entitled:

"The Combination of teachings of Okada 1, Okada 2, Yanamoto or Yonekura with Gibboni or Pick, Babcock, and Brunck Fails to Result in the Claimed Methods"

specifically discusses how the combination of the cited references does not result in the claimed subject matter.

Therefore, it is respectfully submitted that Applicant rebutted the obviousness rejections based on the teachings of the combinations of references after systematically distinguishing each of the cited references from the elements of the instant claims.

2) In response to Applicant's arguments filed October 28, 2002, in which Applicant asserted that none of the references singly or in combination taught or suggested the elements of assessing cell activation and administering cell activation lowering therapy prior to treatment for a disease or for prophylactic purposes, the Examiner rebuts, without providing any support from the cited references, that it is clear from the record that a patient who was going to be treated for a disease would have normal levels checked including, for example, blood pressure and glucose levels to rule out certain other problems. Having

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checked glucose levels, the Examiner alleges that one would have also checked free radical production.

There is no teaching or suggestion in any cited reference that supports the Examiner's reasoning. Glucose overproduction is neither a measure nor indicator of free radical levels in a patient or cell activation. Having checked glucose levels, there is no reference that teaches or suggests that one would then check free radical production as a measure of cell activation. If the Examiner is referring to the teachings of Gibboni *et al.*, it is respectfully submitted that he has misunderstood its teaching. Gibboni *et al.* teaches dyes that are useful for detecting compounds which form hydrogen peroxide as a result of their interaction with an enzyme, such as glucose in the presence of glucose peroxidase, or cholesterol in the presence of cholesterol oxidase. The hydrogen peroxide produced by the interaction of the compound with enzyme reacts with the dye allowing quantitation of the compound (i.e., glucose or cholesterol). The hydrogen peroxide measured is the hydrogen peroxide produced by reaction of the compound with an enzyme, it is not a measure of free radical levels in a patient. Gibboni *et al.* provides no correlation between glucose levels and free radical levels in a patient. Even if it did, that does not suggest a method in which cell activation levels are assessed prior to or with treatment for a disease or as a prophylactic.

Even if there were a correlation, this is irrelevant to the instant claims. The cited art does not teach or suggest that hydrogen peroxide is an indicator of cell activation; it is the instant application that teaches this. The instant methods require the step of assessing cell activation, and if it is high, then, administering activation lowering therapy. The cited art does not teach that it is desirable to check levels of cell activation, nor that lowering such levels prior to treatment or for prophylaxis is desirable.

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As discussed previously and repeated below, the Examiner cannot take official notice of facts outside the record that are not capable of instant and unquestionable demonstration. MPEP 2144.03 states:

The Examiner may take official notice of facts outside of the record which are capable of instant and unquestionable demonstration as being "well-known" in the art. In re Ahlert, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970). . . .

The properties ascribed by the Examiner to bioluminescence are not "capable of instant and unquestionable demonstration as being "well-known" in the art. The Examiner has not cited any art that demonstrates the one of ordinary skill in the art having checked glucose levels would have checked free radical levels.

MPEP 2144.03 continues:

If justified, the examiner should not be obliged to spend time to produce documentary proof. If the knowledge is of such notorious character that official notice can be taken, it is sufficient so to state. In re Malcolm, 129 F.2d 529, 54 USPQ 235 (CCPA 1942). If the applicant traverses such an assertion the examiner should cite a reference in support of his or her position.

In this instance, there is no evidence that knowledge that evidences that one of ordinary skill in the art would check free radicals prior to treatment or as prophylactic. This area of technology is of an esoteric nature, since it is to be used by those in the medical profession. For esoteric technology, MPEP 2144.03 states:

("[A]ssertions of technical facts in areas of esoteric technology must always be supported by citation of some reference work" and "allegations concerning specific 'knowledge' of the prior art, which might be peculiar to a particular art should also be supported." Furthermore the applicant must be given the opportunity to challenge the correctness of such assertions and allegations. **"The facts so noticed serve to 'fill the gaps' which might exist in the evidentiary showing" and should not comprise the principle evidence upon which a rejection is based.**). See also In re Barr, 444 F.2d 588, 170 USPQ 330 (CCPA 1971) (scientific journal references were not used as a basis for taking judicial notice that controverted phrases were art-recognized because the court was not sure that the meaning of the term at issue was indisputable among reasonable

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men); and *In re Eynde*, 480 F.2d 1364, 1370, 178 USPQ 470, 474 (CCPA 1973) ("The facts constituting the state of the art are normally subject to the possibility of rational disagreement among reasonable men and are not amenable to the taking of [judicial] notice.").

In this instance, the Examiner taking judicial notice appears to provide an element of the claims, which is not taught or suggested by any art of record. There is no art of record that suggests that cell activation levels are predictive of anything, and none that suggest methods that include measurement thereof as a prelude to treatment or prophylactically. The Examiner is taking judicial notice of allegations important to the rejection and combining them with a references that do not suggest the claimed element or methods.

In this instance, a reference or references supporting assertions by the Examiner should be provided. No references of record teach or suggest that such tests are ever performed, that treatment options are evaluated based upon the level of cell activation nor that futhan or any compound or regimen should be used prior to therapy for a disease or condition or as a way to improve treatment outcome or reduce risk of treatment nor as a prophylactic.

REBUTTAL TO SPECIFIC ARGUMENTS FROM ACTION DATED JULY 26, 2002

The following remarks were set forth in the Amendment filed October 28, 2002 in response to the Examiner's specific arguments in the Action dated July 26, 2002. In the Action dated January 27, 2003, the Examiner did not address any of the specific arguments presented in Applicant's Amendment. The argument are, thus, submitted again, in modified form, for the Examiner's review.

The Examiner cannot take official notice of facts outside the record that are not capable of instant and unquestionable demonstration. The Examiner makes quite a few such allegations.

1) Without citing any references, the Examiner states that since such patients would normally check their glucose levels, they would be motivated to treat their glucose overproduction if the levels were too high. As noted above,

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there is no teaching or suggestion in any cited reference that supports this statement. Furthermore, even if there were, testing of glucose levels followed by treatment to reduce glucose levels is irrelevant to the instant claims.

Glucose overproduction is not a measure of cell activation, nor is treatment to reduce high glucose a method for reducing cell activation. The instant methods require the step of assessing cell activation, and if it is high, then, administering activation lowering therapy. The cited art does not teach that it is desirable to check levels of cell activation, nor that lowering such levels prior to treatment or for prophylaxis is desirable.

2) The Examiner states that someone who had a trauma would want to know before that condition was treated (if it needed to be treated) by futhan whether or not free radical production had occurred. Again, there is no teaching in any of the cited references nor any art of record that suggests that "someone who had a trauma would want to know [their level of cell activation] before initiating treatment. Again, there is no teaching or suggestion in the cited art for treatment of elevated levels of cell activation, nor for the use of futhan or any compound or regimen therefor. There is nothing of record to support this conclusion; this is based on teachings in the instant application. Furthermore, treatment by futhan in the context of the instant claims is not for treatment of the trauma, but is for lowering cell activation before (or during) treatment for the trauma.

The Examiner is reminded that MPEP 2144.03 states:

The Examiner may take official notice of facts outside of the record which are capable of instant and unquestionable demonstration as being "well-known" in the art. In re Ahlert, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970). . . .

MPEP 2144.03 continues:

If justified, the examiner should not be obliged to spend time to produce documentary proof. If the knowledge is of such notorious character that official notice can be taken, it is sufficient so to state. In re Malcolm, 129 F.2d 529, 54 USPQ 235 (CCPA 1942). If the applicant traverses such an

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assertion the examiner should cite a reference in support of his or her position.

3) It is alleged that the ordinarily skilled artisan would have been motivated to use a compound like futhan after the detection of elevated free radical production by phenol red assay, to treat the patient in an effort to reduce the free radical production. It is respectfully submitted that the claims require administration of treatment to lower cell activation not free radical production. Free radical production simply provides a means of assessing cell activation, it is not the specific target of therapeutic intervention although it may necessarily be reduced upon reducing cell activation. Further, there are no teachings or suggestions in any of the cited references to measure free radical levels as a means to assess cell activation prior to administering therapy for a particular disease or condition, nor as a prophylactic measure nor to reduce the risk of a poor outcome to a treatment, nor is there any suggestion for using futhan to lower cell activation. Furthermore, there is no teaching in any of the references that futhan provides cell activation lowering therapy.

4) The Examiner concludes that it would have been within the purview of the "skilled artisan" to administer the phenol red assay first to detect the free radical production and, if elevated, the measurement would indicate that treatment for the trauma would need to be performed. Such treatment would be the administration of futhan.

First it is noted, that this is **not** what is claimed. According to the instant claims, cell activation levels are assessed, and if the levels are high, then cell activation lowering therapy is commenced. All of this is separate from the treatment for the disease or condition, such as trauma. In fact, if levels are elevated, treatment for the trauma or disease, if possible, might be **delayed** to permit a reduction in the cell activation levels.

Administration of futhan for treatment of trauma, is not what is claimed. The methods involve assessing cell activation levels, and if elevated, administering cell activation-lowering therapy **prior** to performing treatment, or

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administering cell activation-lowering therapy and selecting an alternative treatment. The cell activation lowering therapy is **not** the treatment for the disease (*i.e.*, trauma), but to lower cell activation levels which contribute to poor treatment outcomes and risks of certain diseases. Futhan, if selected as the cell activation lowering therapy, is administered, not to treat the traumatic injury or disease, but to lower the risks of treatment, such as surgery, for the trauma or disease. There is no suggestion in any cited reference to lower levels of cell activation by treatment with futhan or any treatment or regimen; there is no suggestion to assess such levels.

Second, it is noted that the standard for obviousness, is the level of skill of the ordinarily skilled artisan, not the skilled artisan. Second, it is not relevant whether something is within the level of skill of the ordinarily skilled artisan, if the cited references do not teach or suggest the act that is within the level of skill.

5) The Examiner states that it would be routine to assess treatment by administering a phenol red assay because it is well known that phenol red assays are used to detect free radical production, 2) treat trauma with futhan because pancreatitis is well known to be treated by futhan, and 3) use a compound like futhan after the detection of elevated free radical production in an effort to reduce the free radical production because traumas are treated with futhan and traumas produce free radicals. No support for these allegations is provided. Again, the Examiner is reminded that of MPEP 2144.03, which requires documentation to support such statements. As noted above, the instant claims are not directed to methods of treating pancreatitis, but to methods in which levels of cell activation are assessed, and if elevated, are reduced by treatment, not for the underlying disease, but to reduce levels of cell activation.

There is no basis provided for the Examiner's assertion that it would be obvious to use a compound like futhan after the detection of elevated free

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radical production in an effort to reduce the free radical production because traumas are treated with futhan and traumas produce free radicals. The Examiner has provided no reference that teaches or suggests administration of futhan following measurement of cell activation, nor for the purpose of lowering cell activation.

Even if the ordinarily skilled artisan had been motivated to use futhan to reduce free radical production, this is not what is claimed. As noted, the claimed methods require the step of assessing cell activation levels prior to administering therapy for a disease, and then based upon the assessment, administering therapy to lower cell activation levels, not for treatment of any particular disease, and then either with the cell activation lowering therapy or afterward treating the disease.

None of the cited references, singly or in any combination thereof, teaches or suggests a method of improving treatment outcome or the risk of treatment or for prophylaxis by assessing the level of cell activation, determining if the level is high, and then administering cell activation lowering therapy. Thus, the cited references, singly or in any combination thereof, fail to teach or suggest the elements of the claims.

6) The Examiner states that Gibboni *et al.* teaches that phenol red assays are useful for patients to check their cholesterol or glucose levels. This may be correct; there, however, is no suggestion in this or any reference for assessing levels of cell activation. Gibboni *et al.* teaches methods for detecting hydrogen peroxide in a sample; Pick *et al.* teaches a method for assessment of hydrogen peroxide produced by cells in culture, and is of no relevance to the instant claims. Furthermore, the instant claims are not directed to methods for assessing glucose levels, but for assessing cell activation. Glucose levels are not a measure of cell activation.

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Conclusion

The Examiner has failed to set forth a *prima facie* case of obviousness. Not only would there have been no motivation to have combined the teachings of Okada 1, Okada 2, Yanamoto *et al.* or Yonekura *et al.* Babcock *et al.* or Brunck *et al.* with Gibboni *et al.* or Pick *et al.*, The combination of teachings of the references does not result in a method for assessing treatment options or reducing the risk of a treatment outcome or for prophylaxis, by assessing the level of cell activation in a subject, and, if elevated, treating the subject to reduce the levels of cell activation, prior to any further treatment or as a prophylactic measure.

* * *

In view of the above remarks and remarks of record, consideration and allowance of the application are respectfully requested.

Respectfully submitted,
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TRIAGE USING CELL ACTIVATION
MEASURES***

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Michael Lough

MARKED-UP AMENDED CLAIM

Please amend claim 32 as follows:

32. (Twice Amended) A method of prophylaxis, diagnosis and treatment, comprising:

assessing cell activation in a subject; and, if elevated,

administering activation lowering therapy, thereby preventing a disease or disorder or reducing the risk of a poor outcome of treatment of a disease or disorder.